REMARKS

Claims 28, 30, 33, 36-38, 43-44 and 47 are currently pending. Claim 28 is amended to correct a typographical error and not in response to an Examiner's argument or rejection.

In the Office Action mailed on August 13, 2008, the Examiner made a number of rejections, which, for clarity, are listed below in the order in which they are addressed herein.

I. Claims 28, 30, 33, 36-38, 43-44 and 47 stand rejected under 35 USC §103(a) as allegedly being unpatentable over Ohnishi, *et al.*, J. Hum. Genet., Vol 46, pages 471-477 (hereinafter "Ohnishi"), in view of the Cystic Fibrosis Mutation Database (hereinafter "CFMDB") and Fors et al., 2000, Pharmacogenomics. 1:219-229 (hereinafter "Fors"), Mein *et al.*, Genome Research, vol 10, pages 330-343, 2000 (hereinafter "Mein") and Rameckers, *et al.*, (Naturwissenschaften, Vol 84, pages 259-262, 1997) (hereinafter "Rameckers");

II. Claim 28, 33, 36-37,43-44, and 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 10 and 20-21 of U.S. Application No. 11/266,723;

III. Claim 30, and 38 are rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over Claims 10 and 20-21 of U.S. Application No. 11/266,723 in view of the CFMDB;

IV. Claim 28, 33, 36-37,43-44,and 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 of U.S. Application No. 10/967,711;

V. Claim 30 and 38 are rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over Claims 1-7 of U.S. Application No. 10/967,711 in view of the CFMDB.

The Claims Are Not Obvious

Claims 28, 30, 33, 36-38, 43-44 and 47 stand rejected under 35 USC §103(a) as allegedly being unpatentable over Ohnishi in view of the CFMDB, Fors, Mein, and Rameckers.

As discussed below, Applicants respectfully disagree and submit that this combination of references fails to establish obviousness of the claimed embodiments of the invention because, the references teach away from the invention and, even if combined, do not suggest the method

of the instant claims.

Fors teaches away from the claimed invention

As the Examiner notes, Fors teaches the Invader assay offers a simple diagnostic platform to detect single nucleotide changes with high specificity and sensitivity from unamplified, genomic DNA (Office action, page 5). The Examiner asserts that it is not inventive to discover the optimum or workable ranges by routine experimentation (Office action page 7). However, Fors teaches the complete avoidance of amplification cycles, *i.e.*, zero cycles. Thus, the use of *any* PCR cycles, even the limited number of cycles taught in the instant application, does not fall within the "optimum or workable ranges" taught by Fors. As Fors is directed toward describing the benefits of detection without PCR amplification, Applicants submit that Fors on its face teaches away from making the combination with PCR urged by the Examiner.

Ohnishi teaches the use of 35 cycles of PCR prior to Invader assay detection

As noted by the Examiner, and as previously discussed, Ohnishi teaches the feasibility of undertaking genome-wide association studies using blood samples of only 5-10 ml. Ohnishi makes a particular point that such studies require large amounts of DNA (abstract), and Ohnishi teaches the use of *35 cycles* of amplification to in order to reduce the amount of genomic DNA needed for genotyping, even when amplification is followed by Invader assay detection. As stated by Ohnishi, "The greatest advantage of the system described here is the significant reduction in the amount of genomic DNA required for genotyping . . ." (Discussion, page 474). Similarly, Mein teaches the use of 35 cycles of PCR to reduce the amount of genomic DNA needed for typing using the Invader assay. Ohnishi teaches that when 40 ng of genomic DNA (page 472, col. 1) is used in a multiplex reaction prior to detection by the Invader assay, 35 cycles of PCR are still required.

Ohnishi, Mein and Fors, taken together, do not teach or suggest that fewer than 35 PCR cycles should or can can be used, even when the Invader assay is applied as a detection reaction. Rather, they teach the opposite – that, even when the Invader assay is used to amplify detection signal, PCR must still be performed for a large number of cycles.

Rameckers teaches away from the claimed invention

The Examiner asserts that Rameckers cures the deficiencies in the teachings of Ohnishi, Fors, and Mein. In particular, the Examiner asserts that Rameckers teaches PCR for "less than 17 cycles" (office action page 6). Applicants respectfully disagree. Not only does Rameckers not suggest any cycle number *less than* 17, Rameckers does not even suggest that 17 cycles can be used.

The Examiner points out that Eq. 1 of Rameckers is used to describe the PCR process, and claims that Rameckers "illustrates situations using 17 cycles for 100,000 targets" (Office action, page 6). Rameckers does not illustrate this. Rather, Rameckers provides a table (table 1, page 261) and graph (Figure 1, page 260) showing that Eq 1 calculates–mathematically - that 17 cycles would be the required number if 100,000 copies of target were used, and if and ONLY if the amplification efficiency is 1.0, *i.e.*, perfect doubling for each cycle. No calculation presented in Rameckers suggest fewer than 17 cycles.

As the Examiner has highlighted, Rameckers teaches that "the community of PCR users knows from experience that the efficiency of a PCR amplification is 1.0 only in theory "(Office action page 6, citing Rameckers page 259, col. 3). Rameckers goes on to say that, in practice, amplifying intact modern DNA, the average amplification efficiency is close to **0.7**, and still further, Rameckers notes that, if DNA extracts are investigated that contain remnants of inhibiting substances, the amplification efficiency may be lowered remarkably (page 259, col. 3). Rameckers did not achieve detection in 17 cycles, nor does Rameckers even suggest that 17 cycles could be used for actual detection by PCR in a real experiment (as opposed to a theoretical exercise). Rather, Rameckers teaches that 17 cycles is not usable even for 100,000 copies of starting template, because it would require amplification efficiency that is *not achievable* in practice.

Rameckers teaches that the typically recommended amount of DNA for PCR is approx. 1µg of mammalian genomic DNA, which is close to $3x10^5$ templates (300,000) of a single copy target. (page 259, column 1). In contrast, the instant specification teaches using 2 nanograms of genomic DNA for multiplex PCR (see, *e.g.*, Example 9, page 69, lines 22-25). Using the conversion values of Rameckers, the 2 nanograms of DNA taught in the instant specification is about 600 templates. Rameckers provides data for amplifications performed using 100 or 1000

templates. These data show no visible amplification product in any reaction conducted for fewer than 35 cycles (see figure 2), and, when only 100 templates were used, 40 cycles were required to show product (figure 2).

Rameckers concludes that "[T]hese experiments made clear that, not only in theory but also in practice, protocols for amplifications of very small amounts of targets that refer to **cycle numbers of 35 or less are basically useless**." [emphasis added]. This is consistent with the teachings of Ohnishi. While Ohnishi teaches that DNA template can be reduced to 40 ng (page 472, column 1), Ohnishi teaches the use of **35** cycles of PCR amplification for this amount of DNA.

Applicant respectfully submits that Rameckers not only fails to teach or suggest the use of 17 cycles of PCR in real-world assays, but Rameckers also teaches away from the concept of reducing the number of PCR cycles when working with small numbers of template copies. As such, taking the teachings of Rameckers as applied to Ohnishi, Fors, Mein, and the CFMDB, would not be led to configure a reaction with 17 or fewer cycles of PCR prior to detection using the Invader assay. There is nothing in these references to suggest the desirability of doing so, and there are ample teachings indicating that using a small number of PCR cycles is undesirable.

In summary, Ohnishi and Mein teach that 35 cycles should be used to produce large amounts of DNA for multiplex genotyping. Rameckers also teaches that 35 cycles should be used when small amounts of target are used, and teaches that amplification using 17 cycles, even with 100,000 copies of starting template, is not usable because a reaction configured in this way would require amplification efficiency that is not achievable. At best, applying the calculations for real world PCR taught by Rameckers (0.7 typical efficiency for high quality DNA, page 259, col 3) to the teachings of Ohnishi to use 40 ng (12,000 copies) of DNA in a multiplex PCR (page 472, column 1), one of skill the art would be led to use at least approximately 25 to 27 cycles (see Rameckers, Table 1 for 10,000 targets, 0.7 efficiency). Neither Fors nor Mein contravene these teachings.

Applicants respectfully submit that the Ohnishi, CFMDB, Fors, Mein, and Rameckers references, whether taken singly or in any combination, fail to teach or suggest the features of the invention as instantly claimed and therefore fail to establish obviousness of Claims 28, 30,

33, 36-38, 43-44 and 47. Applicants therefore respectfully request that these rejections be withdrawn.

Obviousness-type Double Patenting

II. Claims 28, 33, 36-37,43-44,47 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 10, 20-21 of U.S. Application No. 11/266,723;

III. Claims 30, 38 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over Claims 10, 20-21 of U.S. Application No. 11/266,723 in view of the CFMDB;

IV. Claims 28, 33, 36-37,43-44,47 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 of U.S. Application No. 10/967,711; and

V. Claims 30 and 38 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over Claims 1-7 of U.S. Application No. 10/967,711 in view of the CFMDB.

The two applications cited by the Examiner in making the above-recited obviousness-type double patenting rejections are both substantially later filed than the instant application (which was filed 11/14/03, and which claims priority to yet earlier filed cases). In accordance with the MPEP § 804 I.B.1 procedure regarding provisional double patenting rejections involving earlier and later filed applications, Applicants respectfully request that this double patenting rejection be held in abeyance until such time as a claim is found to be allowable, and that each of these double patenting rejections then be withdrawn from this earlier filed case.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: January 13, 2009

/Mary Ann D. Brow/

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
440 Science Dr., Suite 203
Madison, WI, 53711
608-218-6900